Physical Signs

The adoption of a systematic method for the examination of the thorax was a major achievement in clinical medicine. Early 19th century autopsy reports of lung cancer often gave no indication that the lungs had ever been examined during the course of illness. Many English physicians were skeptical of the practicability of the stethoscope and, particularily, of Laënnec's achievements with it. Auenbrugger's (124) discovery of percussion in the 18th century had made little impression on clinical medicine and auscultation might also have been relegated to oblivion had it not been for the teaching influence of certain English and French physicians.

During the first half of the 19th century practically all the classical symptons and signs of lung cancer were fully established with a few embellishments added in succeeding decades. The specific symptoms of the tumor such as cough, hemoptysis, dyspnoea, and stridor were emphasized by Hughes (13), Bell (125), Bouillaud (34), and Heyfelder (35). The neurologic and vascular syndromes produced by extrapulmonary metastases were described by MacLachlan (14), Hare (11), Burrows (16), Moneret and Fleury (40), and Lanceraux (126). The earliest criteria for the physical diagnosis of lung cancer were developed by Stokes (16) and Graves (17) who identified unilateral dullness and absent breath sounds with bronchial obstruction and alerted

their contemporaries to the significance of mediastinal obstruction in differentiating lung cancer from tuberculosis, pneumonia, and pleurisy. Their observations had also revealed that the physical findings in the thorax were dependent on the size and location of the tumor.

The problem of differentiating lung cancer from other pulmonary diseases by physical diagnosis plagued physicians throughout the 19th century and the quest for the elusive characteristic physical finding continued well into the 20th century. Béhier (127), in 1867, believed he had discovered it in a respiratory murmur which he called "cornage"; Woillez (128), in 1870, described a particular percussion note, "tympanisme thoracique"; Hesse (129), in 1878, identified wheezing with lung cancer; Sée (130), in 1881, emphasized the absence of tactile fremitus; and Witthauer (131), in 1899, relied on thoracic resistance to percussion. In 1912, Adler (116) recommended a variety of tactile maneuvers including "schwellenwerthperkussion", plessimetre percussion, and orthopercussion, and Fishberg and Steinbach (132), in 1921, stressed the association of flatness and absent breath sounds.

An experience in lung cancer developed in the early decades of the 19th century, the inadequacies of physical diagnosis became readily apparent. In 1842, MacLachlan (14) demonstrated that lung cancer could occur with few characteristic symptoms and with no recognizable signs. Smith-Shand (133),

in 1875, summarized the diagnostic frustrations of the era in the British Medical Journal with the comment that despite the large number of publications on lung cancer, the disease still baffled the skill of the physician. During the first three decades of the 20th century, the clinical diagnosis of lung cancer was still dependent on physical signs established almost 100 years previously.

The Sputum Examination

The possibility of diagnosing lung cancer by examination of the sputum was nurtured for a century before coming to fruition in the 1940's with the perfection of Papanicolaou's cytologic technique. The early endeavors by Andral (32) in 1821 and Walshe (15) in 1843 involved microscopic study of expectorated tissue fragments, a procedure which met with very little success because of lack of effective staining methods and the infrequent occurrence of tumor tissue in the expectorate. The difficulties in the microscopic examination of sputum did not deter later investigators from pursuing this approach and in 1887, Hampeln (134) demonstrated that lung cancer could be diagnosed clinically by the examination of expectorated tissue.

The gross characteristics of the sputum were also given considerable attention. Most of the writers on lung cancer were very much impressed with the resemblance of the

sputum to jelly but there was considerable difference of opinion as to which type was pathognomonic. In England, Stokes (10), Hughes (13), and Burrows (16) found the greatest similarity to red currant jelly; in France, Sée (130) thought that the comparison to raspberry jelly was more fitting; in Germany, Janssen (135) identified the disease with grass-green sputum. The concept of a typical lung cancer sputum was generally accepted throughout the 19th century and perpetuated in textbooks in the early decades of the 20th century.

The first significant cytologic studies on sputum were made in 1895 by Betschart (136) who identified cancer cells as large round cells with over-sized nuclei and keratinized cytoplasm occurring singly or in clusters. In 1899, Hermann (137) established criteria for differentiating between malignant squamous cells and benign squamous epithelium commonly desquamated from the buccal cavity. During the same era, Claisse (138), in France, predicted that the cytologic examination of the sputum would eventually provide the means for the early diagnosis of lung cancer but problems in developing suitable staining techniques delayed utilization of the procedure for several decades. Considerable progress was made by Dudgeon and Wrigley (139) in 1935, Wandall (140) in 1938 and Gowar (141) in 1943 but the most important step was the application of Papanicolaou's gynecologic staining technique to the examination of sputum smears.

The introduction of the "Pap" smear and its wide utilization since 1946 added immeasurably to the procedures available for the diagnosis of lung cancer. The technique was readily acquired by pathologists and, in many institutions, the large number of daily examinations requested necessitated the relegation of screening to non-medical personnel. Reports of accuracy have varied with investigators but Papanicolaou (142) found the procedure confirmatory of lung cancer in 90 per cent of his cases and, of particular value, in small tumors not visible on x-ray or accessible to bronchoscopic visualization. It is difficult to assess the role of the "Pap" smear in the increase in lung cancer certification, but it is very apparent that a procedure that is readily performed, widely utilized, and applicable to patients in all stages of the disease, would result in the diagnosis of a great many more cases than was possible prior to 1946.

The X-ray Examination

On November 8th, 1895, Wilhelm Roentgen, college president and amateur physicist, accidently discovered in the basement laboratory of his home that an electrified Crooke's vacuum tube emitted a greenish light capable of penetrating flesh. The early experiments involved chiefly the osseous structures but it was soon realized that the x-ray had possibilities in the examination of the thorax and its contents. In

1901, Weinberger (143) succeeded in producing x-ray pictures of the lung on photographic plates. His article in the Zeitschrift für Heilkunde showed illustrations of lung cancer and photomicrographs of the tumor specimens proving that the diagnosis had been confirmed at autopsy. Further progress in the diagnostic radiology of lung cancer was made by Otten (144) in 1906 but attempts to popularize this form of investigation met with little enthusiasm because of technical difficulties and personal hazards to both patient and physician.

In the United States, Williams (145) was the most active of the early pioneers in chest radiography. His studies demonstrated the usefulness of the x-ray in the differential diagnosis of pulmonary diseases but the importance of his findings was not generally recognized. In 1916, it was proposed at a meeting of the American Sanatorium Association that the x-ray be used in the classification of pulmonary tuberculosis but this suggestion was not finally adopted until 1920. A considerable reluctance to the acceptance of x-ray findings resulted from the numerous failures in developing a standardized technique for x-ray of the chest. Most of the films were overexposed and the images distorted due to lack of proper tube distance and respiratory movements. However, interest in the procedure was sustained by Edison's perfection of the fluoroscope which made it possible to visualize the heart and lungs even though the image could not be successfully recorded om plates.

The x-ray apparatus of the 1920's was a crude instrument with exposed parts capable of producing shocks, burns, and malignant changes. Its wide utilization was limited by its inherent defects and the lack of knowledge regarding its potentialities. As the decade progressed much progress was made in the production of shockproof machines, replacement of glass photographic plates by celluloid film and standardization of x-ray techniques. Sectional radiography was introduced in 1933 as a supplementary diagnostic procedure. In the late 1930's machines began to be produced for mass chest surveys and during recent decades photofluorographic units requiring little technical skill have been installed in countless hospitals, clinics, and health centers screening large segments of the population for lung cancer and other pulmonary diseases. The repeated exposure of millions of adults to x-ray examination has been concurrent with the rapid increase in the diagnosis of lung cancer.

Bronchoscopy

In the closing years of the 19th century Killian (146)(147), devised an instrument by means of which he could directly visualize the bronchi and reported his findings on lung cancer in the Berliner klinische Wochenschrift in 1900. The instrument achieved some degree of popularity in Germany and Mann (148), in 1911, published an atlas with illustrations depicting the diagnosis of bronchogenic carcinoma and other

diseases involving the bronchi. However, technical difficulties and unwarranted anxieties regarding the hazards of the procedure delayed widespread use of bronchoscopy for two decades.

The greatest impetus to bronchoscopy in the early decades of the 20th century was provided by Jackson (149) (150) who established that the procedure was practicable and of invaluable assistance in diagnosis. His clinic in Philadelphia was world famous and by 1930 he had diagnosed 486 cases of lung cancer. The contrast between Jackson's achievements and other means of diagnosis available during that era was very apparent inasmuch as the total lung cancer deaths reported for the entire United States in 1930 was only 2,837. The awareness, in the 1930's, that endobronchial tuberculosis was a common complication of pulmonary tuberculosis led to a more general use of bronchoscopy in tuberculosis sanatoria and hospitals and subsequently, in general hospitals. It was soon realized that the procedure had few contra-indications and was applicable to all pulmonary problems.

In the early decades of this century, bronchoscopic examinations were usually performed by otolaryngologists but in more recent years, the examinations have been also done by thoracic surgeons thereby expanding the availability of the procedure. The vast increase in bronchoscopic examinations is very evident in Smither's (151) report from the Brompton Hospital where only one bronchoscopy was done prior to 1925 and over 800

annually by 1952. During the past three decades bronchoscopy has been frequently performed in all hospitals and has made it possible to diagnose lung cancer in cases presenting clinically as pneumonia, tuberculosis, lung abscess, or pleural effusion. It would be unrealistic not to relate the widespread use of an effective investigative technique with the increase in the number of cases diagnosed.

Thoracic Surgery

At the turn of the century, Benda (152), a German pathologist with particular interest in pulmonary disease, stated that the inaccessibility of the lung precluded the possibility of surgical therapy for lung cancer. This dour prediction did not deter a number of surgeons including Brauer (153), Friedrich (154), Sauerbruch (155) and Willy Meyer (156) from attempting surgical exploration of the thorax. Lenhartz (157) in 1898, reported one successful lobectomy for lung cancer with survival for a year and a half but little progress was made in the succeeding decade. Adler (116) in 1912 recommended exploratory thoracotomy for diagnosis but was very pessimistic about the possibilities of surgical therapy for lung cancer except as a palliative procedure.

Progress in exploratory thoracotomy for lung cancer followed the advances in surgery for non-malignant disease. Heidenhain (158) in 1901 reported the first successful lobectomy

for bronchiectasis and by 1925, there were 85 cases in the literature. However, the operative mortality rate in reported series (159) approximated 60 per cent. Between 1925 and 1935, refinements in technique introduced by Shenstone and Janes (160) and others reduced the surgical hazards considerably and by 1940, experienced surgeons such as Churchill (161) reported mortality rates of less than 4 per cent for lobectomy in non-malignant disease. The first successful pneumonectomy for bronchiectasis was performed by Nissen (162) in 1931.

In 1933, Graham (163) provided the greatest stimulus to the surgical therapy of lung cancer in his report of the first successful pneumonectomy in the Journal of the American Medical Association. It is of historical interest that the patient, a physician, was able to resume his practice and survived more than 25 years. Progress in thoracic surgery was greatly enhanced by experience in World War II which inspired many surgeons to pursue the specialty in civilian life. In the 1940's the thoracic surgeon had many advantages over his predecessors in the form of better anesthesia, antibiotic coverage, blood bank facilities, and newly developed concepts of pulmonary physiology.

The perfection of surgical technique was not correspondingly reflected in increased surgical cures of lung cancer but exploratory thoracotomy vastly increased the opportunities for diagnosis of the disease. As early as 1949, Johnson, et al(164)

reporting on 384 patients with varied pulmonary diseases found 123 cases of lung cancer of which 60 (49 per cent) were diagnosed only by thoracotomy. During the past two decades, exploratomy thoracotomy has become a routine diagnostic procedure in practically all hospitals with relatively few contraindications because of the low operative mortality. It has thus been possible to increase the incidence of lung cancer among cases undiagnosable by other means.

Ancillary Procedures

Lymph node biopsy has become an increasingly popular procedure for differential diagnosis in patients with obscure pulmonary lesions who are unsuitable for exploratory thoracotomy. The biopsies include accessible cervical nodes, scalene nodes, and more recently, mediastinal nodes. The relationship between supra-clavicular adenopathy and abdominal malignancy was established by Virchow in the mid 19th century but the pathways of lymphatic spread from the lung to the neck were not clearly defined until Rouviére's (165) studies in 1938. In 1949, Daniels (166) demonstrated the potentialities of scalene node biopsy and since then this procedure has been performed thousands of times. Gondos and Reingold (167) in a study of 175 proven cases of lung cancer, found 70 (40 per cent) positive scalene lymph node biopsies. In recent years biopsy of mediastinal lymph nodes has been used as a more direct diagnostic approach with considerable

success. It is pertinent that the wide utilization of lymph node biopsy has occurred during the past two decades when the rise in lung cancer has been so striking.

Aspiration biopsy of the lung has been practiced since the 19th century. The procedure was first introduced by Krönig (168) in 1887 under the name of "Probepunktion" (probatory puncture) and also used in Germany by Hellendal (81) in 1889. In the United States, Adler (169) recommended its routine adoption in 1896 but the inaccuracy of results and hazards of spread of the tumor limited its usefulness. In recent years, more accurate localization and specially designed aspiration needles (170) have led to a revival of interest, particularly, in cases not amenable to other forms of diagnostic investigation. A study of lung cancer deaths by Haenzel, et al (171) in 1962 revealed that out of 1,820 cases with microscopic confirmation there were 112 (6.2 per cent) in which the diagnosis had been confirmed by aspiration biopsy. Aspiration of pleural fluid is also used to establish the diagnosis of lung cancer. Prior to the introduction of Papanicolaou's staining technique the procedure consisted of the usual preparation of a cell block from the centrifuged specimen. In recent decades the pleural fluid has also been subjected to cytologic study.

An unrelated diagnostic procedure, the culture of sputum and gastric aspirates for tubercle bacilli, has also led to detection of more cases of lung cancer. Thirty years ago, the

diagnosis of pulmonary tuberculosis would be readily accepted on the basis of x-ray findings even if the sputum were negative for tubercle bacilli. In recent years, the finding of negative cultures in cases suspected of pulmonary tuberculosis has made it obligatory to initiate further investigative procedures.

Accuracy in Diagnosis

It is impossible to ascertain with certainty how much of the recent increase in lung cancer is genuine and how much may be attributed to advances in investigative techniques. Willis (172), contrasting the modest increase in the autopsy incidence of lung cancer in England in the period, 1929-1950, with the tenfold increase in registered deaths, inferred that practically all of the increase was the result of diagnostic progress. There is much evidence to support this contention.

In 1920, there were 956 lung cancer deaths reported in the United States. At that time, the prevailing methods of diagnosis consisted of clinical intuition, physical examination, and the autopsy. During the next decade, the x-ray examination began to be widely used in hospitals and in 1930, there were 2,357 lung cancer deaths reported. Between 1930 and 1940, bronchoscopy was added to the diagnostic routine and thoracotomy was beginning to emerge as a relatively safe surgical procedure. The total lung cancer deaths in the United States rose to 7,121, in 1940.

The succeeding years were characterized by the introduction of the cytological examination of the sputum and bronchial aspirates, the widespread use of exploratory thoracotomy and surgical resection, and mass x-ray examination of the population. In 1950, the total number of lung cancer deaths reported was 18,313. Since then, the tremendous awareness of lung cancer has resulted in an intensification of diagnostic investigation in all pulmonary disorders with particular emphasis on biopsy procedures leading to histologic confirmation. There has also occurred a considerable degree of selectivity in autopsies because of the general interest in lung cancer. The association of public anxiety, medical zeal, and readily available diagnostic facilities has been reflected in a further striking increase of lung cancer deaths with 36,420 reported in 1960, and 50,000 deaths estimated for 1966. The rise in reported lung cancer deaths paralleled the utilization of clinical diagnostic techniques which were virtually non-existent in the early decades of this century.

Statistical studies on the correlation between clinical diagnosis of lung cancer and autopsy confirmation show very clearly how much progress has occurred since the introduction of modern investigative techniques. In a collected series of 178 cases confirmed by autopsy between the years, 1887 and 1900, Sehrt (123) found that only 6 (3.4 per cent) had been diagnosed correctly during life. Ferenczy and Matolcsy (173)

found 18 (22.5 per cent) out of 80 cases diagnosed clinically between 1907 and 1916 and 44 cases (28.5 per cent) out of 150 between 1917 and 1925. A series of 1,070 cases between 1939 and 1949 collected by Farber (174) from 19 hospitals showed a 39 per cent accuracy in clinical diagnosis. During the succeeding decade there was considerable progress in clinical acumen. Halpert (175) (176) reporting on 363 autopsy cases of lung cancer between the years 1949 and 1958 found that 80.7 per cent had been diagnosed correctly during life. The diagnosis had been made by exploratory thoracotomy and/or resection in 88 cases; by bronchial biopsy in 50 cases; by lymph node biopsy in 50 cases; by skeletal muscle or skin biopsy in 25 cases; by needle biopsy of liver or lung in 12 cases; by craniotomy or laparotomy in 11 cases; and by cytologic examination of sputum, bronchial aspirate, or pleural fluid in 15 cases. There were 42 cases without histological or cytologic confirmation in which the diagnosis was made by x-ray examination.

The gradual improvement in diagnostic accuracy during the past 50 years was not limited to the cases confirmed by autopsy which account for only a small proportion of the increase in lung cancer. Haenzel, et al (177) found only 656 (27.5 per cent) of 2,381 cases confirmed by microscopic autopsy; the remainder of the cases had been diagnosed by bronchial, lymph node, or aspiration biopsy; excision of surgical specimen; x-ray examination, or other means. The implication is very clear. It would have been impossible to diagnose the non-autopsied cases a few

decades ago because the methods currently utilized were not available. The assumption that there has been an epidemic rise in lung cancer is, therefore, pure conjecture.

III SIMULATION OF LUNG CANCER BY METASTASES

The widespread utilization of radiology, bronchial and lymph node biopsy, exploratory thoracotomy, and cytology has made it readily possible to detect lung cancer clinically but there are many diagnostic pitfalls inherent in these procedures. Autopsy follow-up has made it increasingly apparent that metastatic tumors may produce findings entirely compatible with the diagnosis of bronchogenic carcinoma.

Magnitude of Problem

One of the earliest demonstrations of metastases simulating bronchogenic carcinoma was reported by Funk (178) in 1930. The case had been diagnosed as primary lung cancer by bronchial biopsy but postmortem examination revealed a primary carcinoma of the pancreas. In 1935, Farrell (179) reported two cases of malignant melanoma and carcinoma of the endometrium respectively, with bronchial involvement producing the type of massive atelectasis found in bronchogenic carcinoma. Maytum and Vinson (180), in 1936, reported a case of hypernephroma with metastatic ulceration into a bronchus. Peery (181), in 1940, reported three cases of extensive bronchial metastasis and

emphasized that malignant involvement of the bronchial mucosa was not an absolute criterion of primary origin. Raine (182), in 1941, found a large papillomatous mass in a bronchus with histologic findings of adenocarcinoma. A subsequent pneumonectomy revealed that the pulmonary tumor had been metastatic to a previously resected carcinoma of the colon.

In 1942, pulmonary metastases from carcinomas of the ovary and thyroid simulating bronchogenic carcinoma were described by Freedlander and Greenfield (183). A case of gastric cancer with metastasis to the left upper lobe was reported by King and Castleman (184) in 1943; the diagnosis of lung cancer had been established by aspiration biopsy and the patient subjected to lobectomy. Leach (185) in 1950 reported three cases of carcinoma of the pancreas erroneously diagnosed as bronchogenic carcinoma; in one of the cases the bronchial biopsy had been positive for lung cancer. In the same year Seiler, et al (186) found that in 17 cases with metastatic bronchial involvement, 10 (59 per cent) had positive bronchial biopsies.

Abbott (187), in 1961, reported 13 cases of endobronchial metastases masquerading as bronchogenic carcinoma. In 1962, Campagna and Greenberg (188) described a case of metastatic carcinoma of the rectum diagnosed as lung cancer by bronchial biopsy. Trinidad, et al (189), in 1963, reported 10 cases of metastatic cancer diagnosed as bronchogenic carcinoma by biopsy or cytologic examination. The subsequent autopsies

revealed 4 carcinomas of the pancreas, 3 carcinomas of the kidney, 2 adrenal cancers, and 1 lymphosarcoma. A review of 104 autopsy cases of carcinoma of the pancreas by Lisa, et al (190) in 1964 revealed that 12 cases (12 per cent) had been diagnosed during life as bronchogenic carcinoma; in 9 of the cases there had been histologic confirmation by biopsy. The features of carcinoma of the pancreas favoring simulation of primary lung cancer were the high incidence of metastases to the lung and to the mediastinal, tracheobronchial, and paratracheal lymph nodes. Thoracic metastases occurred most frequently in carcinomas of the tail of the pancreas which remained silent for long periods of time thereby adding to the possibility of erroneous diagnosis.

Bronchiolo-alveolar (alveolar cell) carcinoma has been generally accepted as an adenocarcinoma of the lung characterized by peripheral origin and a distinctive histologic appearance. In 1946, Herbut (191) challenged this concept and reported 6 cases of metastatic lung cancer showing the typical alveolar propagation identified with bronchiolo-alveolar carcinoma. The primary tumors were located in the rectum, colon, pancreas, and gall bladder, respectively. Similar observations were made by Eck (192) in 1955 and Johnsen and Olsen (193) in 1957. In 1961, Rossman and Vortel (194) collected 20 cases of metastatic lung cancer with the bronchiolo-alveolar pattern and added 5 cases of their own. Hewer (195), in the same year, reported 4 cases secondary to carcinoma of the pancreas; in 2 of the cases the

primary tumors were very small and had not been detected on the first gross examination of the tissues.

The duplication of the distinctive histologic features of bronchiolo-alveolar carcinoma by metastases from extrathoracic carcinomas has significant clinical importance. Unless there is autopsy exclusion of other primary sites, the diagnosis can not be made with certainty. There has been a progressive rise in the reported incidence of this tumor in the past few decades. In 1942, Neuberger and Geever (196) found only 25 cases in the literature; in 1949, Swan (197) compiled an additional 27 cases and added 9 cases of his own; and in 1957, Eck (198) recorded 337 cases. In 1961, Bell and Knudtson (199) found the tumor to occur in 8 per cent of primary lung cancers. Reports of incidence have varied and the tumor has been diagnosed under many names ranging from malignant pulmonary adenomatosis to peripheral adenocarcinoma. Mimicry of bronchiolo-alveolar carcinoma by metastases makes it impossible to make an absolute diagnosis on the basis of biopsy or resected surgical specimen.

In an attempt to assess the magnitude of the problem of metastatic simulation of bronchogenic carcinoma, Rosenblatt, et al (200), in 1966, reviewed the autopsy protocols and clinical records of 380 cases of extrathoracic carcinoma. Pulmonary metastases occurred in 50 per cent. More than 10 per cent of the extrathoracic carcinomas had been erroneously diagnosed clinically as primary lung cancer with cytologic and/or histologic

confirmation in two-thirds of the cases. Carcinoma of the pancreas presented the greatest source of diagnostic error and carcinoma of the kidney was next in frequency. The other primary sites were breast, adrenal, endometrium, prostate, colon, stomach, thyroid, larynx, ovary, and esophagus. In a recent study of 194 pulmonary malignancies diagnosed by bronchial biopsy, Lemoine, et al. (261) found 101 cases (52 per cent) of metastatic disease, mostly secondary to cancer of the breast and uterus.

Causes of Diagnostic Errors

The factors found chiefly responsible for the erroneous histologic diagnosis of bronchogenic carcinoma were (a) metastatic involvement of the larger bronchi and (b) pleomorphism of the lung and lymph node secondary growths. Invasion of the bronchial wall by way of the subepithelial lymphatics led to the formation of coalescing tumor masses which eventually ulcerated through the epithelium and formed polypoid projections into the lumen. Bronchoscopic visualization revealed a tumor apparently arising from the bronchial mucosa and a biopsy positive for malignancy confirmed the incorrect diagnosis. Metastatic involvement of the bronchi also produced positive findings of cancer cells in the sputum and bronchial aspirates.

Extrathoracic ductal or glandular carcinomas often presented squamoid features in metastatic lesions of the lymph nodes or lungs. Crowding and proliferation of the malignant cells in the new environment produced the effect of cells arranged in sheets giving the appearance of undifferentiated

squamous carcinoma. These metastatic foci did not have the characteristic features of a true squamous carcinoma such as keratinization or pearl formation but the resemblance was sufficient to cause diagnostic confusion, particularly, in frozen tissue sections. Adenocarcinomas metastasizing to the alveolar structures first proliferated along the walls but eventually filled the alveolar spaces. The ultimate effect was that of a broad sheet of malignant squamous cells in which evidence of metastatic origin was obtainable only by special staining techniques or meticulous search for ductal or glandular structures.

In many instances, the certification of bronchogenic carcinoma on death certificates has been based only on the x-ray examination. This is a major diagnostic pitfall. It is customary to think of pulmonary metastases as presenting bilateral nodular densities, linear striations, or pleural effusions on the x-ray films but metastases may also present as unilateral solitary shadows or atelectatic areas comparable to densities observed in bronchogenic carcinoma. These latter effects are usually produced by involvement of the larger bronchi with endobronchial obstruction.

Validity of Certification

The vast majority of certifications of lung cancer are not based on autopsy confirmation but on procedures by which it may not be possible to differentiate between primary and

secondary lung cancer. The affinity of the lung for metastases therefore creates a large potential for diagnostic error.

In a study of 2,381 lung cancer deaths among white males Haenszel, et al (171) found that 656 (27.5 per cent) of the cases had been diagnosed by autopsy and that 1,725 (72.5 per cent) had been diagnosed by other means. There were only 625 cases (26.2 per cent) diagnosed by biopsy of a surgical specimen. Among the remaining cases the diagnosis was made by bronchial biopsy in 288 (12.1 per cent); by biopsy of a metastatic site in 139 cases (5.8 per cent); and by aspiration biopsy in 112 cases (4.7 per cent). The diagnosis had been made on x-ray evidence, alone, in 418 cases (17.5 per cent). There was also a miscellaneous group of 143 cases (6 per cent) in which the diagnosis of lung cancer was based on autopsy without microscopic examination (35 cases); on clinical findings only (35 cases); and for reasons "not stated" (75 cases).

In a similar study among white females, Haenszel and Taeuker (177) found that out of 749 cases certified as dying of lung cancer only 134 (18 per cent) had microscopic autopsy confirmation and 615 cases (82 per cent) were diagnosed by other methods. There were 183 cases (24.4 per cent) with biopsy of a surgical specimen; 82 cases (11 per cent) with aspiration biopsy; 63 cases (8.4 per cent) with bronchial biopsy; and 51 cases (6.8 per cent) with biopsy of a metastatic site. There were 171 cases (22.8 per cent) diagnosed by x-ray examinations and 56 cases

certified on the basis of "clinical findings only" or reasons "not stated". The remaining 9 cases had autopsies without microscopic examination of the tissues.

The above mortality studies are presumably representative of the procedures used throughout the United States in the diagnosis of lung cancer. They show that approximately one fourth of the white male cases and one third of the white female cases had been certified as dying of lung cancer without any histologic confirmation, whatsoever. It is also evident that among the male cases with histologic examination, almost twice as many had veen validated by biopsy as compared with autopsy; among the female cases with histologic examination, almost three times as many cases had been validated by biopsy.

In a study of death certification of lung cancer in Leeds, Bonser and Thomas (201) found that out of 953 cases, only 267 (28 per cent) were confirmed by autopsy. There were 210 cases (22 per cent) in which the diagnosis was based on clinical histology. There were 456 cases (47.8 per cent) in which the diagnosis was made without any histological confirmation and, in 47 of these, the diagnostic data was limited to history and physical examination. Of considerable interest was a special study of the autopsied cases which showed that 10 per cent had been erroneously diagnosed as bronchogenic carcinoma on the death certificates. If this study is representative of lung cancer certification in England, the vast majority of cases certified as

dying of primary lung cancer did not have autopsy confirmation and almost 50 per cent did not have any histological confirmation.

The approximately 300,000 annual deaths from cancer in the United States provide a large potential for the erroneous diagnosis of bronchogenic carcinoma. Many of these diagnostic errors are corrected at autopsy but this information does not affect the official mortality statistics which are usually based on clinical data. There are no procedures readily available for the amending of death certificates nor is modification encouraged by municipal, state, or national authorities. In the customary order of events, the certificate is made out immediately after the death of the patient and the case is processed by the local health department. Time is required for the performance of a meticulous autopsy and, regardless of the final results, the disease is classified as primary lung cancer in the official vital statistics and tumor registries because of the original certification.

Accuracy in lung cancer mortality data requires a careful study of all biopsy material including resected lungs. The differentiation between primary and secondary lung cancer is often difficult and at times, infeasible. The harried hospital pathologist seldom has the time to scrutinize surgical specimens for stigmata of metastases and is apt to diagnose bronchogenic carcinoma on the basis of squamoid features of the tumor, bronchiolo-alveolar appearance, or endobronchial masses resulting from secondary lymphatic invasion.

The autopsy is the most accurate method for confirming the diagnosis of bronchogenic carcinoma but this important procedure is often delegated to inexperienced assistants or residents whose knowledge of the pathologic manifestations of bronchial and pulmonary metastases is very limited. Solitary tumors involving the larger bronchi are readily identified as primary lung cancers without attempting to establish bronchial origin or carefully examining the other organs for possible inconspicuous primary sites. Multiple disseminated lesions are often classified as primary lung cancer because of the failure to establish an extrathoracic primary origin. The validity of mortality data on lung cancer is dependent on the adherence to rigid histologic criteria in both the biopsy and autopsy diagnosis of bronchogenic carcinoma.

In the evaluation of the epidemic rise in lung cancer, three related phenomena should be considered -- (1) the vast majority of cases have been diagnosed by biopsy and x-ray examination, (2) the increase in lung cancer has been concurrent with the widespread utilization of these procedures, and (3) autopsy follow-up has shown that there are many diagnostic pitfalls in these procedures. Biopsy and x-ray examinations have accounted for most of the cases detected during recent decades and have also been responsible for erroneous diagnoses because of the mimicry of bronchogenic carcinoma by metastases from extrathoracic carcinomas.